EPA Reviewer: Chris Schlosser, M.F.S. **Signature**: _____
Risk Assessment Branch VI, Health Effects Division (7509P) **Date:** _____
EPA Secondary Reviewer: Nancy McCarroll **Signature**: _____
Risk Assessment Branch VI, Health Effects Division (7509P) **Date:** _____

Template version 09/11

TXR#: 0056765

DATA EVALUATION RECORD[1]

STUDY TYPE: Carcinogenicity – mice, feeding
OPPTS 870.4200b [§83-2b]; OECD 451.

PC CODE: 016331 **DP BARCODE:** D410187

TEST MATERIAL (PURITY): Momfluorothrin (95.7% a.i.)

SYNONYMS: S-1563

CITATION: Rached, E. (2012). S-1563: 78-Week Oncogenicity (Feeding) Study in the CD-1 Mouse. Harlan Laboratories Tld, Itingen, Switzerland. Harlan Study #C76177, July 18, 2012. MRID 49020022. Unpublished.

SPONSOR: Sumitomo Chemical Company, Ltd.

EXECUTIVE SUMMARY:

In a carcinogenicity study (MRID 49020022) momfluorothrin (95.7% a.i., Batch 9CM0109G) was administered to CD-1 mice (52/sex/dose) in the diet at dose levels of 0, 600, 2500, or 5500 ppm (equivalent to 0, 72, 308, or 673 mg/kg bw/day for males, and 0, 99, 433, or 934 mg/kg bw/day for females) for 78 weeks. Additionally, an interim sacrifice satellite group of 12/sex/dose was administered the test-substance for 52 weeks.

No treatment related effects were observed on mortality, clinical signs, hematology, or gross pathology.

Significant decreases in body weight and body weight gain were observed in males in the mid- and high-dose groups (BW: -11% and -18%, respectively) treated for 78 weeks. In interim sacrifice animals, males showed a significant decrease in body weight at the high-dose only (-15%). No effects were observed on female body weights after 52 weeks of treatment.

Significantly increased absolute (up to 45%) and relative (up to 55%) liver weights were identified in all dose groups for males and females in the mid- and high-dose groups following 78-weeks of treatment. In the liver, increased incidences of hepatocellular hypertrophy were observed in the mid- and high-dose groups of both sexes. Additionally, brownish pigment and single cell necrosis were observed in the high-dose groups.

1 Disclaimer: The attached Data Evaluation Record is a modified version of the Tier II Summary provided by Sumitomo Chemical Co. Ltd. Portions of this document may have been altered by the EPA reviewer.

The LOAEL is 2500 ppm (308/427 mg/kg bw/day), based on significant decreases in body weights in males, and increases in liver weights and increased incidence of hepatocellular hypertrophy and single cell necrosis in both males and females. The NOAEL is 72/99 mg/kg bw/day.

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased body weights and liver effects in male rats.

This carcinogenicity study in mice is **Acceptable/Guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice. The lack of stability data was noted as a minor deficiency. However, this is not expected to impact the results of the study.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIAL AND METHODS

1. Test Material Momfluorothrin
Description: Not stated
Lot/Batch: 9CM0109G
Purity: 95.7%
CAS#: 609346-29-4
Stability: Expiry date: 22 February 2012 (after completion of treatment)

2. Vehicle Basal diet. Water was added as an aid to pelleting.

3. Test Animals
Species Mouse
Strain CD-1 (Crl:CD1(Icr, SPF))
Age Approximately 6 weeks at the start of treatment
Weight 22.8-34.7 g (males), 18.5 – 26.4 g (females)
Source Charles River Germany, D-97633 Sulzfeld, Germany.
Acclimation period 7 days
Diet Pelleted standard Kliba Nafag 3433 rodent maintenance diet (Provimi Kliba AG, 4303 Kaiseraugst /Switzerland) *ad libitum*
Water Tap water was available *ad libitum*
Housing Individually in Makrolon type-2 cages with wire mesh tops and sterilized standard softwood bedding.
Environmental conditions
Temperature 22 ± 3ºC
Humidity 30 to 70%
Air change Minimum 10 - 15 air changes per hour
Photoperiod 12 hour light / dark cycle

B. STUDY DESIGN:

1. In life dates: 25 Mar 2010 – 4 Oct 2011

2. Animal assignment/dose levels: Animals were assigned by body weight stratification using a computer-generated algorithm to the test groups noted in Table 1.

TABLE 1: STUDY DESIGN

Test group	Conc. in diet (ppm)	Dose to animal (mg/kg/day [M/F])	Main study 78 weeks (Allocation A)		Interim sac. 52 weeks (Allocation B)	
			Male	Female	Male	Female
Control	0	0	52	52	12	12
Low (LDT)	600	72/99	52	52	12	12
Mid (MDT)	2500	308/433	52	52	12	12
High (HDT)	5500	673/934	52	52	12	12

3. **Dose selection:** The dose levels were selected based on the results from a 13-week oral feeding study (study not provided) where administration of up to 7000 ppm resulted in decreased body weights at 4500 and 7000 ppm, and hepatocellular necrosis at 7000 ppm.

4. **Diet preparation and analysis:** Diet was prepared every 3 weeks by mixing appropriate amounts of test substance with Kliba Nafag 3433 rodent maintenance diet and was stored at room temperature (20 ± 5ºC). Homogeneity and stability were tested on all dose groups prior to first administration. During the study, samples of treated diet were analyzed at least every 3 months for stability and actual concentration.

Results:

Homogeneity analysis (%RSD): 0.4 to 8.2

Stability analysis: Stability of the test item was verified for up to 28 days at room temperature (data not provided).

Concentration analysis (%nominal): 81.6 to 119.4

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** All data were collected electronically and are conserved on a magnetic medium. Individual values were rounded before printing. All derived values that appear in tables represent the rounded results of calculations that used the exact raw data value. The following statistical methods were used to analyze food consumption, body weight, clinical laboratory data, mortality, organ weights and ratios, macro- and histopathology data: If the variables can be assumed to follow a normal distribution, the Dunnett test (many to one T-test) based on a pooled variance estimate was applied for the comparison of the treated groups and the control groups for each sex; The Steel (many-one rank) test was applied instead of the Dunnett's test when the data could not be assumed to follow a normal distribution; The Cox regression model was used to analyze mortality data; Macro- and histopathology incidence data were analyzed, where appropriate, using the Fisher's Exact Test; Non-neoplastic lesion incidence in the liver was analyzed where appropriate using the Armitage-Cochran Trend test; Tumor incidences were analyzed for the carcinogenicity groups where appropriate using the Peto test.

C. METHODS:

1. **Observations:**

   1a. Cageside observations: Animals were inspected twice daily for signs of toxicity and mortality.

   1.b Clinical examinations: Clinical examinations were conducted once daily, with detailed clinical examinations performed weekly including palpation for tissue masses.

2. **Body weight:** Animals were weighed weekly until week 14, and every 3 weeks from week

15 to the end of the study.

3. **Food consumption and compound intake:** Food consumption for each animal was determined at the same time as body weights.

4. **Ophthalmoscopic examination:** Not conducted.

5. **Hematology and clinical chemistry:** Blood was collected under isoflurane anesthesia from all allocation B animals after week 52 and from all allocation A animals after week 78. Animals were not fasted prior to sampling. The CHECKED (X) parameters were examined.

   a. Hematology:

	Hematocrit (HCT)	X	Leukocyte differential count*
	Hemoglobin (HGB)		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)		Mean corpusc. HGB conc.(MCHC)
	Erythrocyte count (RBC)		Mean corpusc. volume (MCV)
	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Minimum required for carcinogenicity studies (Cont. and HDT unless effects are observed) based on Guideline 870.4200 and OECD 451

   b. Clinical chemistry*: Not conducted.

6. **Urinalysis*:** Not Conducted.

7. **Sacrifice and pathology:** All organ and tissue samples from all animals of the control and high dose groups, all decedents, and all gross lesions, were processed and embedded, sectioned and stained with haematoxylin and eosin, and microscopically examined by the study pathologist. Livers from mid- and low-dose animals were also processed and examined as a target organ of the test item.

   In addition, sections of liver from 2 animals in both sexes each of the control and high dose groups were stained with PAS reaction, Schmorl's stain and Perl's stain. and examined histopathologically. Organs indicated above were weighed prior to fixation on the day of necropsy at scheduled sacrifices. Terminal bodyweight was recorded immediately prior to necropsy, and organ to bodyweight ratios were calculated. The CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta, thoracic*	XX	Brain (multiple sections)*+
X	Salivary glands*	XX	Heart*+	X	Periph.nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (retina, optic nerve)*
X	Jejunum*	X	Thymus	X	GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*	X	UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroids*
X	Rectum*	X	Urinary bladder*	X	Thyroids*
XX	Liver*+	XX	Testes*+	X	OTHER
X	Gall bladder* (not rat)	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct* (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicle*	X	Skin*
X	RESPIRATORY	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	XX	Uterus*+		
X	Lung*++	X	Mammary gland*		
X	Nose*				
X	Pharynx*				
X	Larynx*				

* Required for carcinogenicity studies based on Guideline 870.4200.
+Organ weight required in carcinogenicity studies.
++Organ weight required if inhalation route.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** No treatment-related signs of toxicity were observed throughout the study.

2. **Mortality:** No treatment-related mortality was observed during the study.

B. BODY WEIGHT: Significant decreases in body weight and body weight gain were observed in males in the mid- and high-dose groups treated for 78 weeks. No decreases in female body weights were observed (Table 2). In Allocation B animals, males showed a significant decrease in body weight at the high-dose only (-15%). No effects were observed on female body weights after 52 weeks of treatment (Not shown in table).

TABLE 2: Mean bodyweights (BW) and bodyweight gains (BWG) of animals treated for 78 weeks[a]

g±SD]	Dietary Concentration (ppm)			
	0 (C)	600	2500	5500
MALES Initial BW	28.78 ± 1.74	29.13 ± 2.02	29.07 ± 1.89	28.29 ± 1.92
Final BW	51.64 ± 4.94	50.94 ± 7.64	45.54 ± 5.12** (-11.8%)	41.89 ± 3.40** (-18.89%)
BWG Wk[1] 1	7.70 ± 5.99	6.82 ± 5.45	7.65 ± 6.38	4.12 ± 6.33** (-46.50%)
BWG Wk 1-13	48.12 ± 12.50	42.15 ± 10.79*	40.71 ± 12.45** (-15.4%)	35.12 ± 9.45** (-27.02%)
BWG Wk 1-26	66.42 ± 17.86	58.05 ± 15.40*	51.42 ± 17.07** (-22.59%)	44.71 ± 10.43** (-32.69%)
BWG Wk 1-52	76.83 ± 20.12	68.44 ± 18.65*	54.59 ± 18.52** (-28.95%)	46.19 ± 11.16** (-39.89%)
Overall BWG Wk -1-78	80.73 ± 20.40	74.77 ± 23.32	57.32 ± 18.87** (-29%)	48.81 ± 13.75** (-39.54%)
FEMALES Initial BW	22.55 ± 1.29	22.20 ± 1.49	22.25 ± 1.48	21.50 ± 1.50** (-4.66%)
Final BW	34.52 ± 5.03	34.03 ± 5.34	32.64 ± 4.06	33.03 ± 3.76
BWG Wk 1	4.54 ± 7.717	2.87 ± 6.58	3.35 ± 6.14	7.48 ± 8.86
BWG Wk 1-13	30.38 ± 11.79	27.40 ± 11.77	30.72 ± 8.83	35.29 ± 11.55
BWG Wk 1-26	42.12 ± 17.17	40.10 ± 15.76	37.30 ± 12.72	43.65 ± 14.83
BWG Wk 1-52	52.18 ± 20.70	51.60 ± 27.57	42.66 ± 13.50*	48.20 ± 14.48
Overall BWG Wk -1-78	53.13 ± 21.60	53.48 ± 22.98	47.62 ± 20.05	53.69 ± 18.02

% C = Percent from control
[a] Data obtained from pages 362-397 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.
1) Results are presented as % of initial body weight.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Food consumption for high-dose animals treated for 52 or 78 weeks was decreased at several treatment intervals throughout the study period. Mean values from Allocation A animals showed decreases by 15 and 10% for males and females, respectively. This decrease was considered to be treatment-related. Data for low- and mid-dose animals were considered to be similar to controls.

2. **Compound consumption (time-weighted average):** Test item intake from Allocation A animals was calculated to be 72, 308, or 639 mg/kg/day in males; and 99, 427 or 853 mg/kg/day in females, respectively.

3. **Food efficiency:** Not reported.

D. OPHTHALMOSCOPIC EXAMINATION: Not conducted.

E. BLOOD ANALYSES:

1. **Hematology:** No treatment-related effect on hematology parameters were noted in either sex in the main or satellite groups. Decreased WBC and corresponding differential counts apparent in females of all treated groups in the main group were considered to be not treatment-related, as there was no dose-dependency and the values were within the range of

historical controls.

2. Clinical chemistry: Not conducted.

F. URINALYSIS: Not conducted.

G. SACRIFICE AND PATHOLOGY:

1. Organ weight: Significantly increased absolute and relative liver weights were identified in all dose groups for males, and females in the mid- and high-dose groups following 78-weeks of treatment. In Allocation B animals, significantly increased liver weights were observed in both sexes at the mid- and high-dose levels at 52 weeks (Shown in Table 3).

Other statistically significant changes in absolute or relative organ weights, particularly in spleen or kidney, were considered incidental.

TABLE 3. Liver weights after 52 and 78 weeks of treatment

Organ	Dietary concentration (ppm)			
	0	600	2500	5500
Males				
Absolute weight (g)				
52 Weeks	2.25 ± 0.49	2.67 ± 0.73	2.48 ± 0.24	2.75 ± 0.28* (+22.22%)
78 Weeks	2.33 ± 0.34	2.61 ± 0.71* (+12.02%)	2.58 ± 0.44* (+10.73%)	2.97 ± 0.40** (+27.47%)
Relative to body weight (%)				
52 Weeks	4.54 ± 0.67	5.02 ± 0.59	5.59 ± 0.43** (+23.12%)	6.57 ± 0.51** (+44.71%)
78 Weeks	4.65 ± 0.68	5.37 ± 1.49** (+15.48%)	5.85 ± 0.71** (+25.81%)	7.22 ± 0.69** (+55.27%)
Females				
Absolute weight (g)				
52 Weeks	1.54 ± 0.27	1.67 ± 0.14	1.85 ± 0.21** (+20.13%)	2.24 ± 0.17** (+45.45%)
78 Weeks	1.65 ± 0.28	1.64 ± 0.29	1.91 ± 0.37** (+15.76%)	2.35 ± 0.49** (42.42%)
Relative to body weight (%)				
52 Weeks	4.61 ± 0.51	5.06 ± 0.64	5.83 ± 0.58** (+26.46%)	7.03 ± 0.32** (+52.49%)
78 Weeks	4.77 ± 0.77	4.90 ± 0.62	5.89 ± 0.79** (+23.48%)	7.15 ± 1.06** (+49.89%)

Data obtained from pages 403-419 of the study report.
[1]Values are group means ± SD
Values in parentheses are percent differences from controls, calculated by the reviewer
*p < 0.05, ** p < 0.01

2. Gross pathology: No treatment related macroscopic finding were reported in either sex.

3. Microscopic pathology:

a. Non-neoplastic: In the liver, significant increases in the incidence of hepatocellular hypertrophy were observed in a dose-dependent manner in the mid- and high-dose groups of both sexes (Shown in Table 4). Significantly increased hepatocellular hypertrophy was also observed in Allocation B females at the mid- and high-doses (Not shown in Table).

Additionally, brownish pigment and single cell necrosis were observed in the high-dose groups.

TABLE 4. Incidence (# affected/severity) of selected non-neoplastic microscopic lesions in organs of male and female mice treated with momfluorothrin in the diet for up to 78 weeks. [a]

	Dose (ppm)			
Lesion	**0**	**600**	**2500**	**5500**
Males				
Liver				
Hepatocellular hypertrophy	12/1.8	12/1.3	35/1.6**	32/1.0**
Brownish Pigment	0	0	0	13/1.0
Single Cell Necrosis	0	0	0	4/1.0
Females				
Liver				
Hepatocellular hypertrophy	4/1.5	2/1.5	37/1.6**	47/2.3**
Brownish Pigment	0	0	0	21/1.0**
Single Cell Necrosis	0	0	1/1.0	2/1.0

a Data were obtained from page 1419 of the study report.
n = 52 (50 for low-dose females)
* Significantly different ($p<0.05$) from the control group
** Significantly different ($p<0.01$) from the control group

b. Neoplastic: No treatment related neoplastic lesions were reported in either sex.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: Based on the results of this study, S-1563 is not oncogenic in mice. Liver abnormalities in both sexes at 2500 and 5500 ppm, decreased body weight gain in males at 2500 and 5500 ppm and decreased food consumption in both sexes at 5500 ppm were observed as toxicologically significant changes. Therefore, a no-observed-adverse-effect level (NOAEL) for S-1563 was established at 600 ppm in both sexes, corresponding to 72 mg/kg body weight/day in males and 99 mg/kg body weight/day in females.

B. REVIEWER COMMENTS: Treatment with S-1563 resulted in decreased body weights, increased liver weights, and increased incidence of hepatocellular hypertrophy in male rats at 2500 and 5500 ppm. Increases in liver weights at 600 ppm were not considered to be toxicologically relevant as no corresponding histopathology was identified and the dose is below the level leading to carcinogenicity in rats. Additionally, brownish pigment and single cell necrosis were observed in both sexes at 5,000 ppm. No treatment-related changes in body weights or body weight gain were observed for female rats.

The LOAEL is 2500 ppm (308/427 mg/kg bw/day), based on significant decreases in body weights in males, and increases in liver weights and increased incidence of hepatocellular hypertrophy and single cell necrosis in both males and females. The NOAEL is 72/99 mg/kg bw/day.

C. STUDY DEFICIENCIES: Minor deficiency: Stability data not provided.